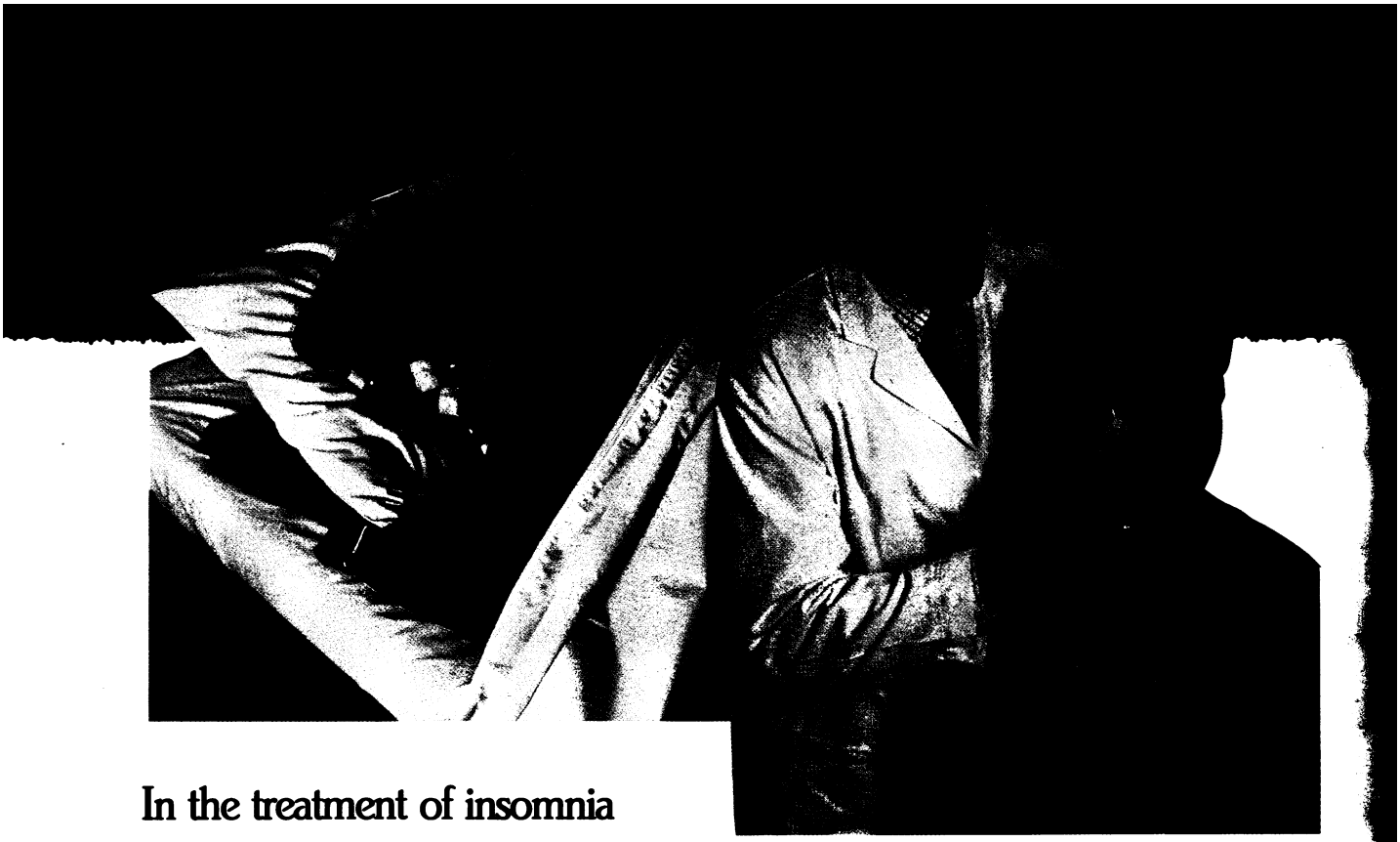


In the treatment of insomnia

Good mornings start with restful nights.

Dalmane *(flurazepam HCl/Roche)* patients fall asleep faster, sleep longer and seldom awaken with morning hangover.

Feeling well rested in the morning usually means having slept well the night before. And for insomniac patients receiving hypnotic therapy, a good morning also means awakening with few side effects from their medication. Many physicians choose Dalmane for their patients who suffer from insomnia for this very reason.

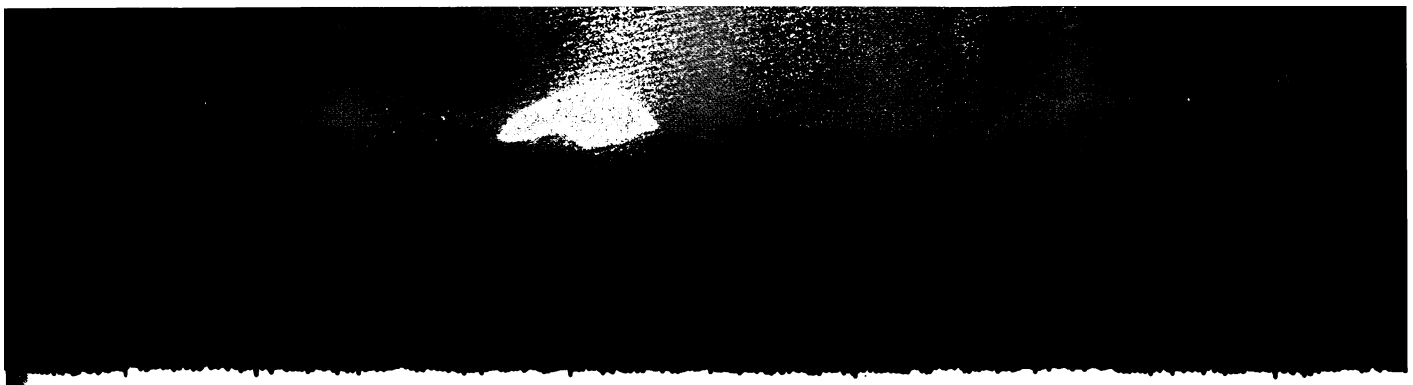
Aside from enabling patients to fall asleep more quickly and sleep longer, Dalmane seldom causes morning hangover. Most Dalmane patients feel alert and refreshed when they awaken. In 53 paired-night clinical studies comparing Dalmane and placebo in 2010 insomniac patients with a variety of secondary diagnoses, most Dalmane patients awakened more alert and refreshed, and less groggy and drowsy, than on nights when they had taken only placebo.[1] In a double-blind crossover study of 42 patients in private practice, approximately three ti as many patients reported feeling refreshed and alert awakening after a night on Dalmane (flurazepam/Ro compared to placebo nights.[2] This difference was hig significant ($p<0.001$). And a retrospective study of hospitalized patients who received Dalmane revealed a 3.1% incidence of side effects.[3]

While residual effects from Dalmane therapy ar infrequent, patients should be cautioned about drinkin alcohol, driving or operating hazardous machinery af ingesting the drug.

Efficacy and safety in a broad range of patient types.

Over 2000 clinical trials involving more than 10,000 patients have shown that Dalmane patients asleep sooner, sleep longer and experience fewer noct awakenings.[4] The safety and efficacy of Dalmane hav been demonstrated in medical and surgical hospitalize patients, in patients seen in office practice and in elder patients.[5-8] Since the risk of oversedation, dizziness, co

ROCHE®



n and/or ataxia increases with larger doses in the elder- it is recommended that the dosage be limited to 15 mg.

Moreover, the efficacy and safety of Dalmane for the atment of insomnia have been demonstrated in thou- nds of patients with a variety of primary medical condi- ns, including cardiovascular, neuropsychiatric, endocrine- tabolic, gastrointestinal, genitourinary, respiratory and sculoskeletal disorders.[1] Dalmane (flurazepam HCl/Roche) contraindicated in pregnancy and in patients hypersensi- e to the drug.

voids rebound insomnia pon discontinuation.

Rebound insomnia—a worsening of sleep beyond etherapy levels after drug discontinuation—has been ported as a potential clinical problem with some hypnot- .[9,10] However, this problem has not been reported with almane. In eight out of eight sleep laboratory studies, re were no reports of rebound insomnia.[11] When you scribe Dalmane, you can be confident of efficacy that hances therapeutic progress. Your insomniac patients can assured of a restful night, night after night—a good start a good morning.

References: **1.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **2.** Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971. **3.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **4.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **5.** Meyer JA, Kurland KZ: *Milit Med 138*:471-474, Aug 1973. **6.** Feffer HL, Gibbons B: *Med Times 101*(8):130-135, Aug 1973. **7.** Jacobson A *et al: Psychophysiology 7*:345, Sep 1970. **8.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **9.** Kales A, Scharf MB, Kales JD: *Science 201*:1039-1041, Sep 1978. **10.** Kales A *et al: JAMA 241*:1692-1695, Apr 1979. **11.** Monti JM: *Methods Find Exp Clin Pharmacol 3*(5):303-326, 1981.

For efficacy from the beginning to the end of therapy

15-mg/30-mg capsules

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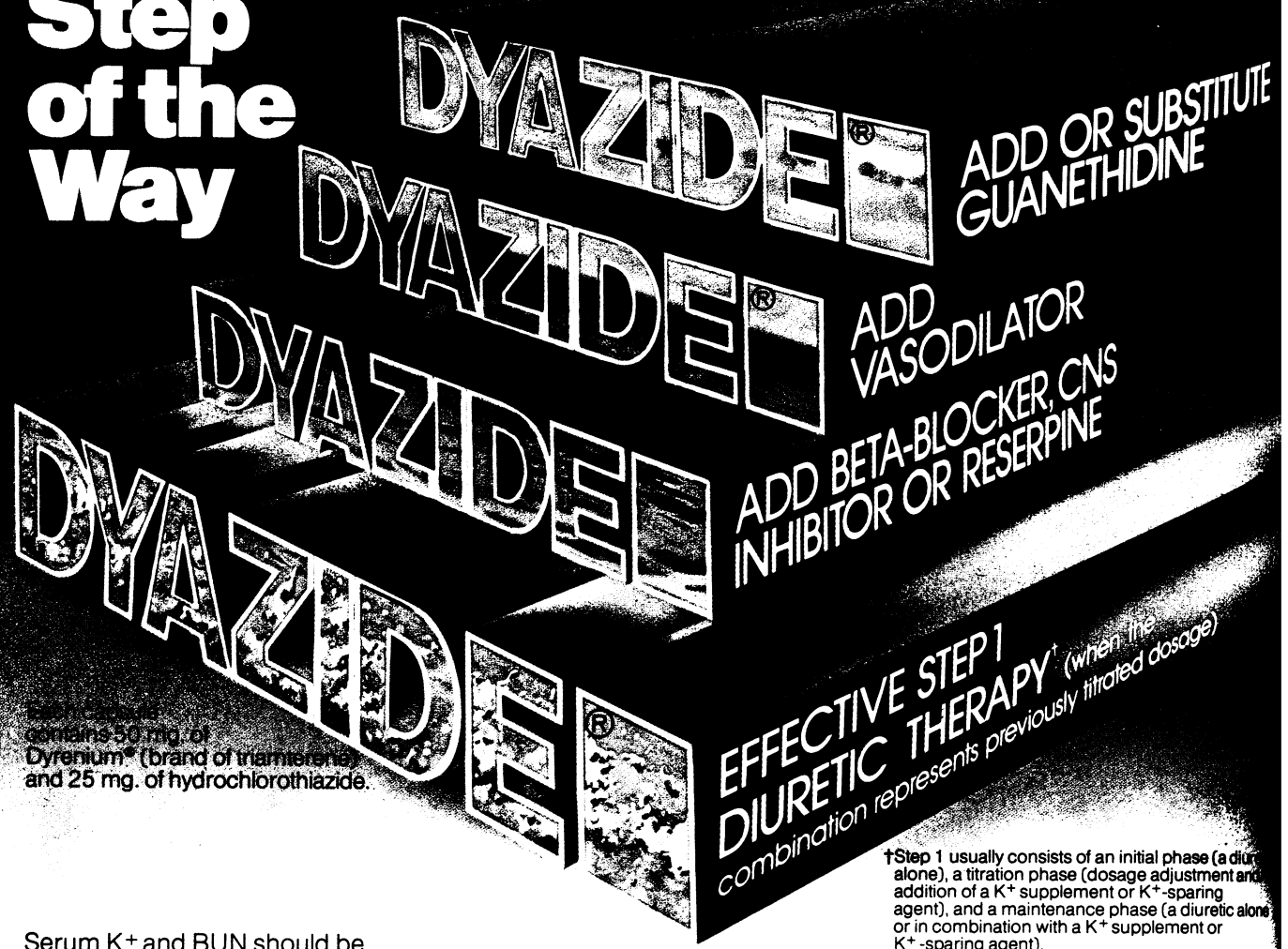

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and addition of a K^+ supplement or K^+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this comoination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Package (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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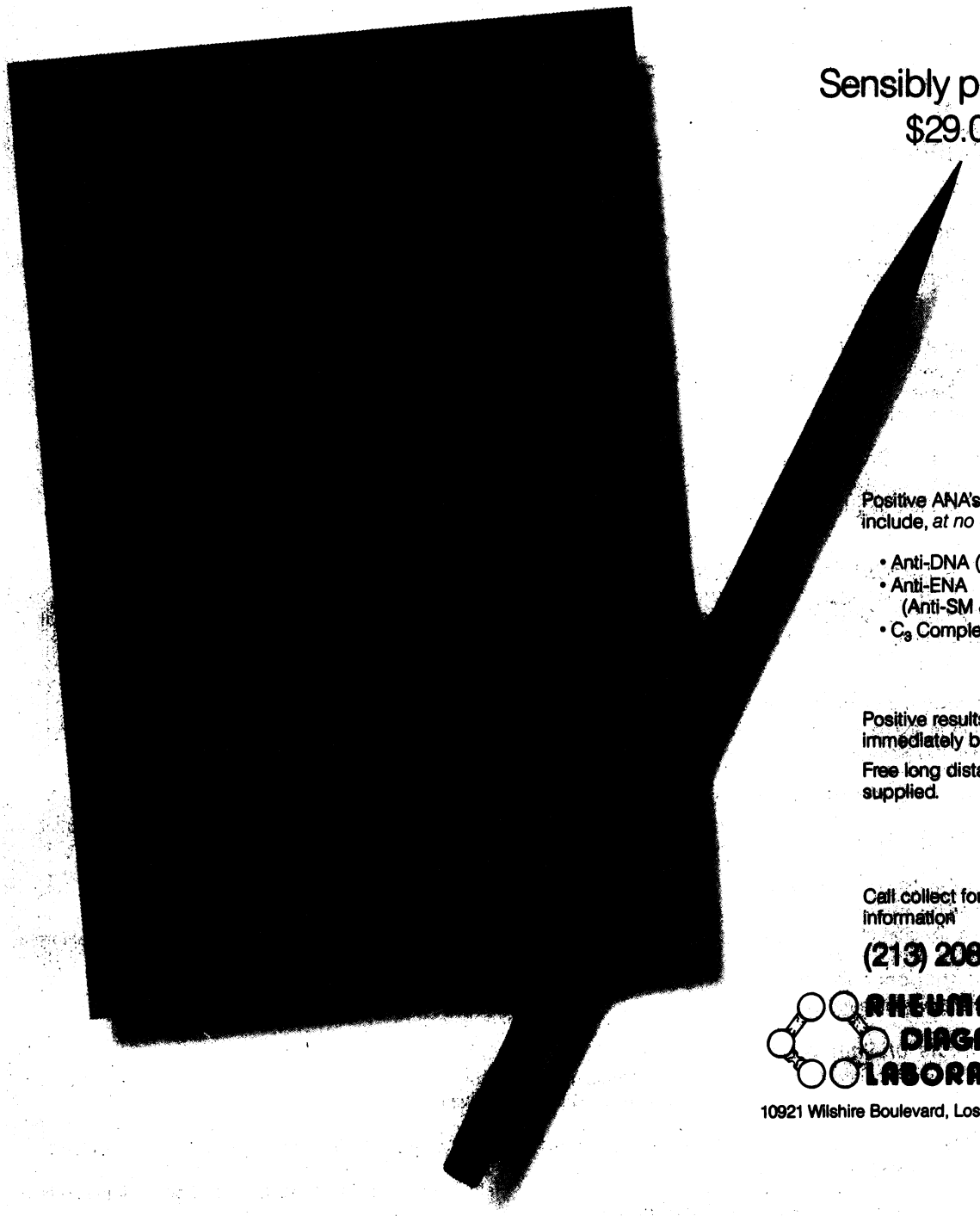

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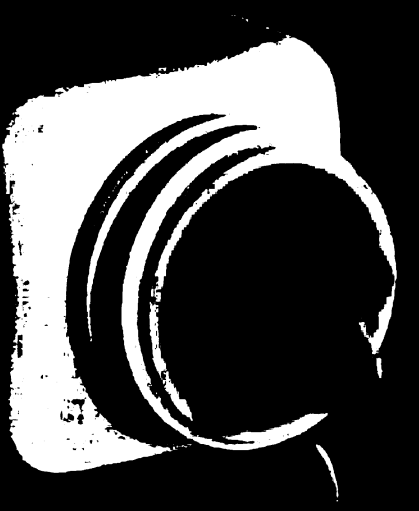

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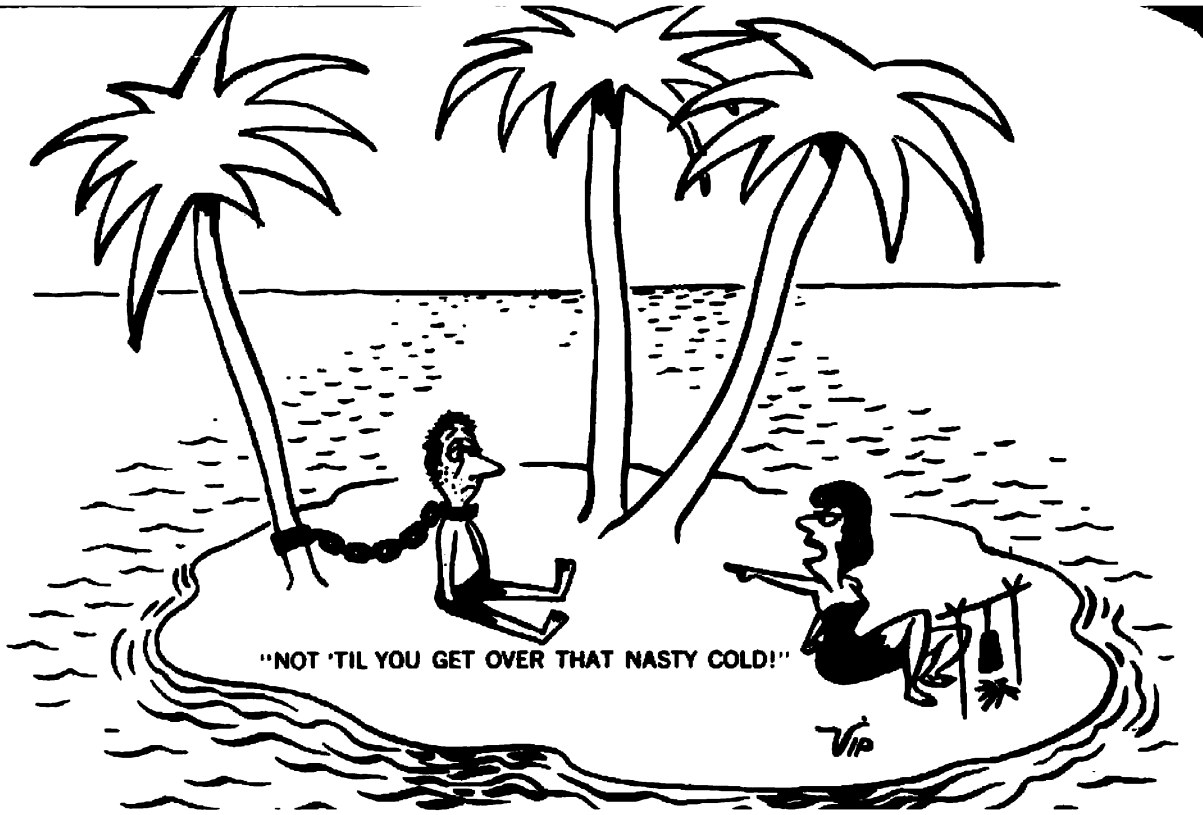

Citra®Forte Syrup stops stubborn coughs

. . . and with an Rx for CITRA® FORTE Capsules you can provide the additional benefits of helping your patients "feel well" for the duration of their colds — free of most cold symptoms.

CITRA® FORTE SYRUP (C III)

Each 5cc contains:

Hydrocodone Bitartrate	5 mg.
(WARNING: May be habit forming)	
Ascorbic Acid	30 mg.
Pheniramine Maleate	2.5 mg.
Pyrilamine Maleate	3.33 mg.
Potassium Citrate	150 mg.

PRECAUTIONS: Patients should be advised to avoid using machinery or driving until response to antihistamines is established. Use with caution in patients with idiosyncracies to formula ingredients

CITRA® FORTE CAPSULES (C III)

Hydrocodone Bitartrate	5 mg.
(WARNING: May be habit forming)	
Ascorbic Acid	50 mg.
Pheniramine Maleate	6.25 mg.
Pyrilamine Maleate	8.33 mg.
Chlorpheniramine Maleate	1 mg.
Phenylephrine HCl	10 mg.
Salicylamide	227 mg.
Caffeine Alkaloid	30 mg.
Acetophenetidin	120 mg.

PRECAUTIONS: Patients should be advised to avoid using machinery or driving until response to antihistamines is established. Use with caution in patients with idiosyncracies to formula ingredients.
CITRA FORTE CAPSULES should be used with caution in patients with hypertension, cardiac disease, diabetes or hyperthyroidism.
WARNING: This preparation may damage the kidneys when used in large amounts or for a long period of time. Use with caution in greater than recommended dose or regularly for longer than 10 days (Acetophenetidin).

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- Digolase . . . Digestive enzymes
- Glytinic Tablets and Liquid . . . Iron plus aminoacetic acid for iron deficiency anemia
- Triva Douche Powder . . .
  Oxyquinoline Sulfate 2.0%, Alkyl Aryl Sulfonate 35.0%, Sodium Sulfate 52.5%, Disodium EDTA .33%.
  Treats all three types of vaginitis

Rx • Triva Jel . . .
Per 5 grams: oxyquinoline benzoate 7.5 mg.; alkyl aryl sulfonate 62.5 mg.; disodium edetate 2.5 mg.; aminacrine HCl 10 mg.; copper sulfate .063 mg.; sodium sulfate 6.9 mg.
Provides Continuous action

Rx • Triva Combination . . . Jel and Powder kit

Precaution
If irritation occurs at the onset of treatment with Jel, treatment may be postponed for a day or two and preliminary treatment with ½ strength Triva Douche used. Regular treatment should then be resumed.

Boyle & Company/
Pharmaceuticals
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(answers upside down below)

1. The California Medical Association's 112th Annual Session will be held March 11-16, 1983 at _____.
2. Over 40 CME accredited courses featuring modern solutions to today's medical problems are available for physicians of all _____.
3. Professional liability, Medi-Cal and private contracting are among the many controversial issues to be discussed at CMA's policy-making _____.
4. An opportunity to view the latest in commercial and scientific technology is available in the _____.
5. A first time feature at Annual Session will be the showing of nine award winning _____.
6. Physicians and guests may save time by pre-registering before _____.

Answers: 1. the Westin Bonaventure Hotel, Los Angeles. 2. specialties. 3. House of Delegates. 4. Exposition Hall. 5. medical films. 6. February 11, 1983 (but you can register at the door).

If you didn't get the word, clip, complete and send this form to:

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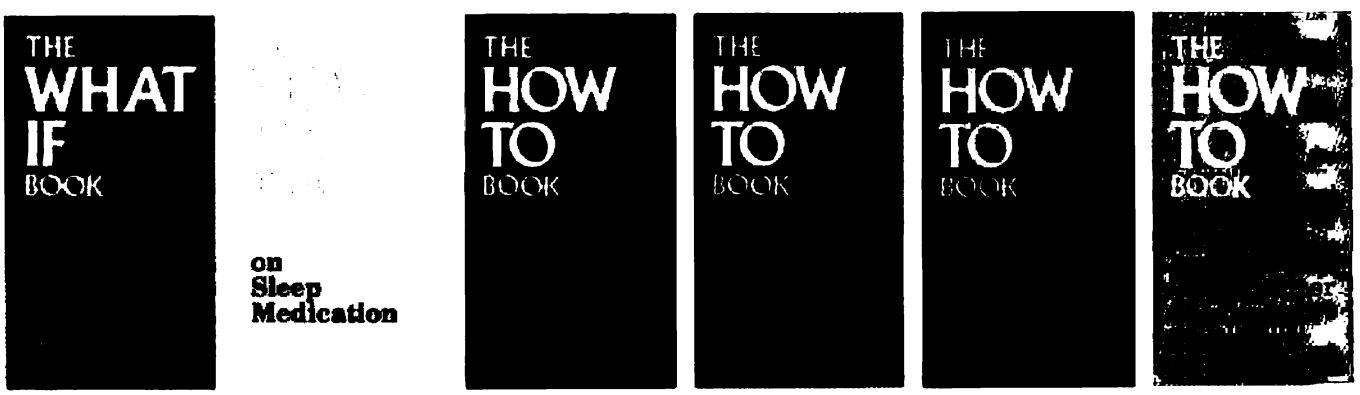

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IF YOU ARE A PHYSICIAN, YOUR RISK* OF CONTRACTING HEPATITIS B IS...

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For many physicians the risks are unavoidable...

*based on prevalence data from a seroepidemiologic survey of medical specialties

For a Brief Summary of Prescribing Information, please see last page of this advertisement.

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Hepatitis B:

The consequences are unpredictable

Although hepatitis B is an unpredictable disease with a variety of presentations and outcomes, most patients recover. Persistence of viral infection (the chronic carrier state) occurs in 5 to 10 percent of persons who become infected with hepatitis B virus. Acute hepatitis B infection may be symptomatic and can incapacitate a person for weeks to months or lead to complications or chronic sequelae. However, 50 to 60 percent of all hepatitis B infections are subclinical, asymptomatic, and usually undetected. These cases have a greater risk of progression to chronic sequelae.

Sequelae of hepatitis B

Chronic carrier state	Develops in up to 10% of patients who have had hepatitis B; occurs more frequently in anicteric cases.[2] Chronic carriers are usually asymptomatic but may develop other chronic sequelae
Chronic persistent hepatitis	Generally a benign condition; progression to cirrhosis or other late sequelae such as hepatoma is rare[3]
Chronic active hepatitis	A major late complication; occurring in approximately 3% to 5% of cases[4]
Cirrhosis	An estimated 11% of deaths due to cirrhosis are associated with hepatitis B[5]
Liver cancer	The relative risk of primary liver cancer for carriers is 273 times greater than for noncarriers[5]

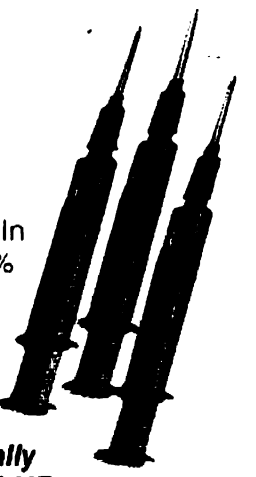
For susceptible individuals at increased risk of contracting hepatitis B infection...

Merck Sharp & Dohme announces

NEW Heptavax·B®

(Hepatitis B Vaccine | MSD)

Now...the disease is preventable



Highly immunogenic

Clinical studies[6-8] have shown HEPTAVAX-B to be highly immunogenic. In one study, HEPTAVAX-B induced neutralizing antibody (anti-HBs) in 96% of vaccine recipients following the three-dose regimen.[6]

Highly effective

In clinical studies, HEPTAVAX-B was highly effective in protecting vaccine responders against acute hepatitis B, asymptomatic infection, and the chronic carrier state. In these studies,[6,7] ***the vaccine was virtually 100% effective in preventing hepatitis B in those who developed anti-HBs.***

Incidence of adverse reactions did not differ significantly from placebo

Generally well tolerated

In over 6,000 individuals administered HEPTAVAX-B during clinical trials since 1975, no serious adverse reactions attributable to vaccination were reported. In two double-blind, placebo-controlled studies[6,7] involving a total of 2,485 persons, the overall rates of adverse reactions reported by the vaccine recipients did not differ significantly from those of placebo recipients.

Injection-site soreness is the most common adverse reaction. Less common local reactions are erythema, swelling, warmth, or induration which usually subside within 48 hours.

Low-grade fever (less than 101°F) occurs occasionally and is usually confined to the 48-hour period following vaccination. Although uncommon, fever over 102°F has been reported.

Systemic complaints, including malaise, fatigue, headache, nausea, dizziness, myalgia, and arthralgia, are infrequent and have been limited to the first few days following vaccination. Rash has been reported rarely.

MSD
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For a Brief Summary of Prescribing Information, please see last page of this advertisement.

NEW Heptavax·B® Vials, 3 ml
(Hepatitis B Vaccine | MSD)

for you...
for your staff...
for your patients...

"Persons at substantial risk of HBV [hepatitis B virus] infection who are demonstrated or judged likely to be susceptible should be vaccinated."[9]

—Recommendation of the Immunization Practices Advisory Committee (ACIP)[9]

The Immunization Practices Advisory Committee (ACIP) has identified certain populations at risk of HBV infection and has recommended vaccination for appropriate members, as follows:

ACIP recommendations for vaccination against hepatitis B infection[9]

- health-care workers
- hospital staff
- clients and staff of institutions for the mentally retarded
- hemodialysis patients
- homosexually active males
- illicit injectable drug users
- recipients of certain blood products
- household and sexual contacts of HBV carriers
- classroom contacts of deinstitutionalized mentally retarded HBV carriers who behave aggressively
- special high-risk populations from areas where hepatitis B is highly endemic
  - Indochinese and Haitian refugees
  - Alaskan Eskimos
- inmates of long-term correctional facilities

A complete copy of the ACIP recommendations is available through your MSD Professional Representative.

A NEW AGE IN THE CONTROL OF ANGINA

R

(NIFEDIPINE) *Capsules 10 mg*

PROCARDIA is the beginning of a new age in the treatment of angina.

The Calcium Age.

[illegible]

[illegible]

Through this action, PROCARDIA manages:

—vasospastic angina, by preventing coronary artery spasm and increasing myocardial O_2 supply

—classical effort-associated angina, by dilating peripheral arteries to reduce afterload and myocardial O_2 demand

—mixed angina, which involves elements of vasospastic and effort-associated angina

Like beta blockers, PROCARDIA reduces myocardial O_2 demand. But unlike these agents, PROCARDIA also increases myocardial O_2 supply to both normal and poststenotic areas of the myocardium by preventing coronary artery spasm.

PROCARDIA

THE FIRST ORAL CALCIUM CHANNEL BLOCKER

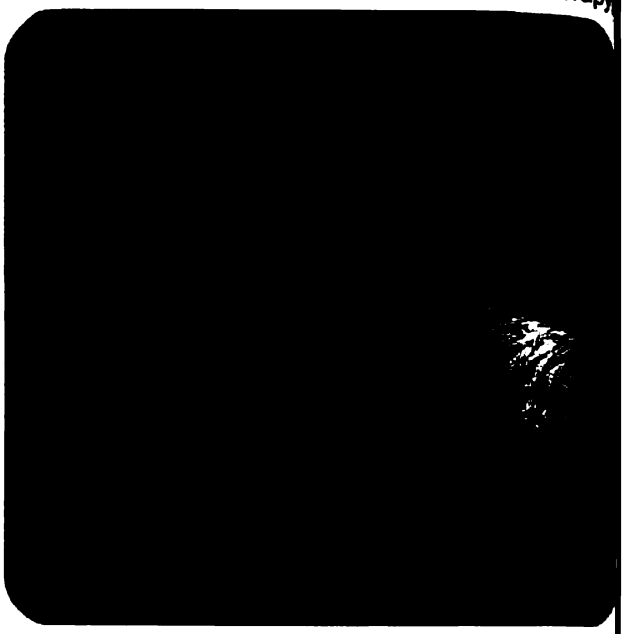
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

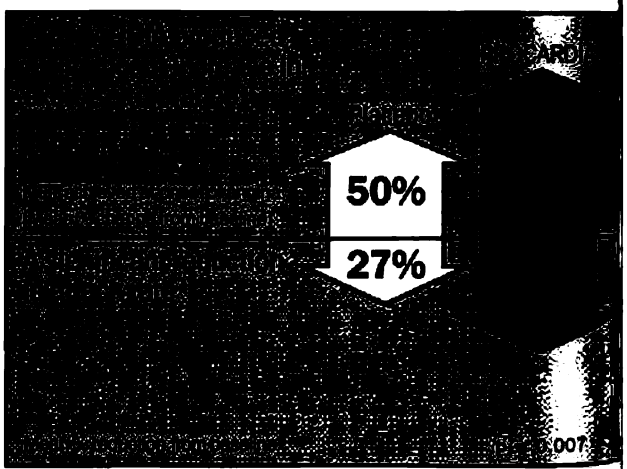
PROVEN EFFECTIVE ACROSS THE SPECTRUM OF ANGINA

Contemporary medical opinion holds that the pathophysiology of angina is a spectrum ranging from pure, fixed atherosclerotic lesion to pure coronary artery spasm. Many patients, however, are believed to have a combination of both lesion and spasm.[2,3]

Angina due to pure fixed lesion can be prevented by reducing oxygen demand. Angina due to coronary artery spasm can be treated by preventing the spasm itself, thereby increasing oxygen supply. With this new understanding of angina, optimal antianginal therapy should provide this dual action: increasing O_2 supply while reducing O_2 demand.

In effort angina*
(when symptomatic despite conventional therapy)





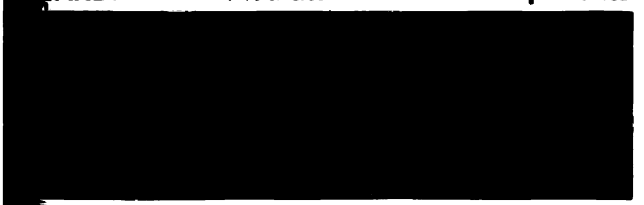
Double-blind, placebo-controlled, crossover 20-week study of 32 patients (27 evaluated for attack rate; 19 for exercise tolerance). Mean PROCARDIA dosage: 51 mg/day.

*In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete

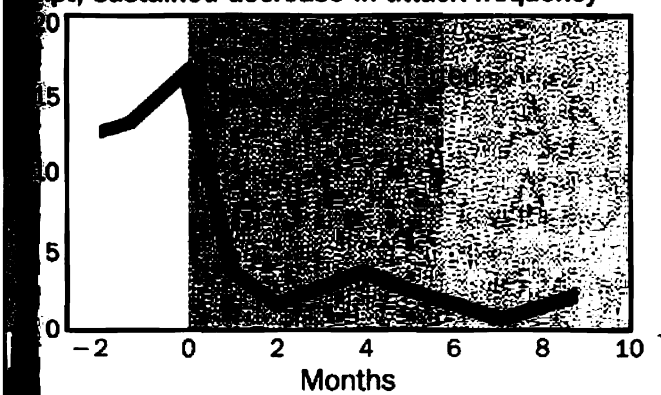
Please see PROCARDIA Brief Summary on last page.

asospastic angina

CARDIA eliminated attacks in 63% of patients[5]

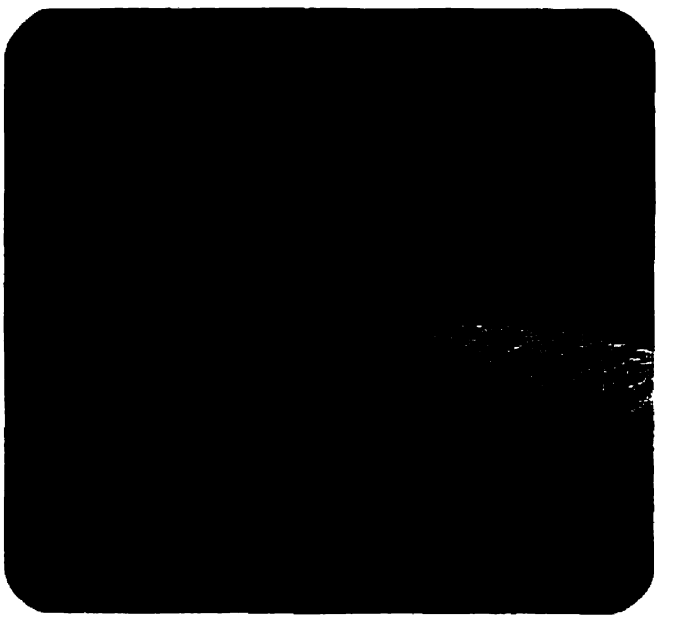


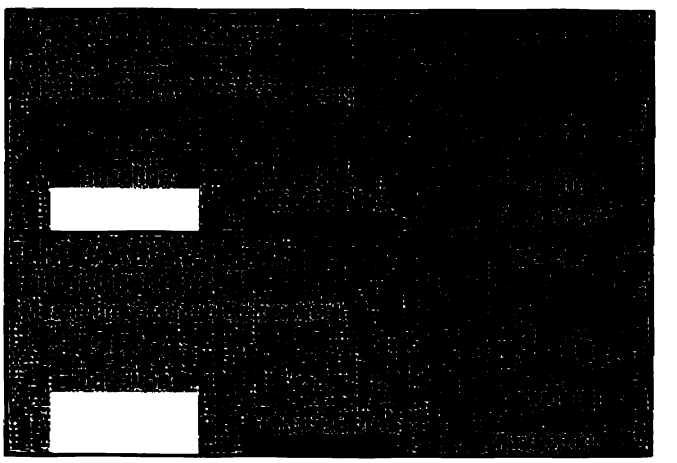
pt, sustained decrease in attack frequency[6]



term, open study of 127 patients unresponsive to beta ers and/or nitrates with symptoms of myocardial mia and demonstrated coronary artery spasm. ARDIA dosage: 40 to 160 mg/day.

In mixed angina (fixed lesion and spasm)





Studies of patients with mixed angina characterized by pain at rest and effort. Most patients (89%) were initiated on nitrate and/or beta blocker therapy but remained symptomatic. Minimum duration of nifedipine treatment two months. Nifedipine dosage: 30 to 120 mg/day.

PROCARDIA®
THE FIRST ORAL CALCIUM CHANNEL BLOCKER

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

ANGINA MANAGEMENT BEYOND BETA BLOCKERS

—Beta blockers prevent angina primarily by lowering myocardial oxygen demand. Like these agents, PROCARDIA reduces myocardial oxygen demand. However, PROCARDIA provides an added dimension of angina control by increasing myocardial oxygen supply where coronary artery spasm is present.

—Beta blockers can actually cause spasm. PROCARDIA prevents spasm.

—Beta blockers decrease myocardial perfusion in poststenotic areas. PROCARDIA increases myocardial perfusion to both normal and poststenotic areas.

—Beta-blocker treatment is limited in patients with myocardial dysfunction, COPD, asthma, bundle branch blocks, and diabetes. PROCARDIA can be given safely in all these groups of patients.

—The hypotensive effect of PROCARDIA is usually modest and well tolerated, however, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or subsequent upward dosage adjustment, and may be more likely with concomitant beta blockers.

—Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA, or at the time of dosage increases. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers, if possible, rather than stopping them abruptly before beginning PROCARDIA.

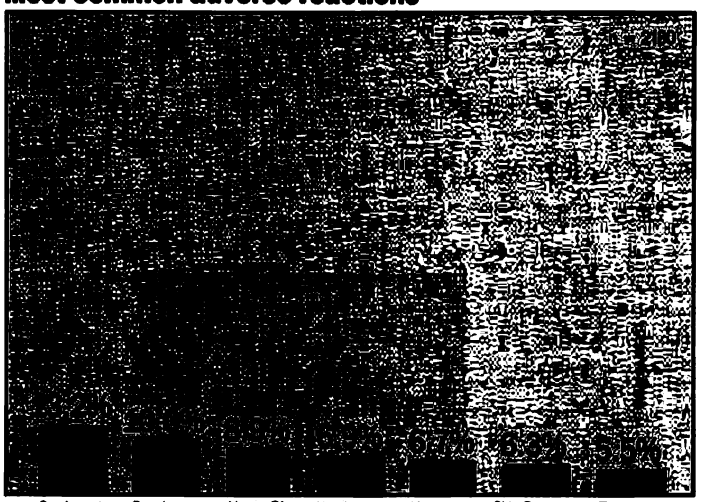
—Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

Please see PROCARDIA Brief Summary on last page.

THE FIRST ORAL CALCIUM CHANNEL BLOCKER...

PROVIDES PROTECTION WITH A MILD SIDE-EFFECT PROFILE

Most common adverse reactions



Information is drawn from a large uncontrolled experience in 2180 patients and presents the most frequent side effects reported with PROCARDIA.

AN ADDED ADVANTAGE: COMPATIBILITY

—MAY BE USED WITH A WIDE VARIETY OF OTHER AGENTS

—CAN BE USED WITH NITRATES AND BETA BLOCKERS WITH CAUTION (See Warnings and Precautions)

THE FIRST ORAL CALCIUM CHANNEL BLOCKER FOR THE MANAGEMENT OF ANGINA

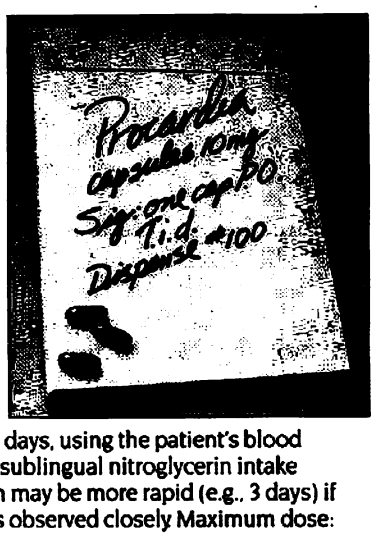
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Proven effective when used alone.

Enhanced effectiveness when combined with beta blockers.

Convenient dosing

Start with:	1	10-mg capsule *t.i.d.*
Titrate to:	2	10-mg capsules *t.i.d.*
Titrate to:	3	10-mg capsules *t.i.d.*



For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely. Maximum dose: 180 mg/day.

References

1. Lichtlen PR, Engel H-J, Wolf R, et al: Regional myocardial blood flow in patients with coronary artery disease after nifedipine. in Lichtlen PR, Kimura E, Taira N (eds): *International Adalat® Panel Discussion: New Experimental and Clinical Results* Tokyo, Excerpta Medica, 1978, pp 69–85.
2. Maseri A, Chierchia S: Angina pectoris—a new dimension, a new approach: Part 2. *Primary Cardiol* 6:123–136, October 1980.
3. Braunwald E: *Introduction: New Concepts in Ischemic Heart Disease: The Role of Coronary Artery Spasm*. New York, Science & Medicine, Inc, 1980, p 1.
4. Mueller HS, Chahine RA: Interim report of multicenter double-blind, placebo-controlled studies of nifedipine in chronic stable angina. *Am J Med* 71:645-657, October 1981.
5. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: experience in 127 patients. *N Engl J Med* 302:1269–1273, June 5, 1980.
6. Braunwald E (moderator): Procardia® (nifedipine) in clinical practice. Presented at symposium following the Thirty-First Annual Scientific Session of the American College of Cardiology, Atlanta, Georgia, April 29, 1982.

PROCARDIA® CAPSULES
(nifedipine)

For Oral

BRIEF SUMMARY

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiographic evidence the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., when pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate these agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that this combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Pregnancy: Category C.

ADVERSE REACTIONS: The most common adverse events include dizziness, light-headedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. One single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contains 10 mg of nifedipine. PROCARDIA Capsules are supplied in amber glass bottles of 100 capsules (NDC 0069-2600-66).

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

Pfizer LABORATORIES DIVISION
PFIZER INC.

The Problem

SYMPTOMS:

EARLY INTERSTITIAL CYSTITIS

- irritative voiding symptoms
- suprapubic pain
- functional bladder capacity reduced
- anatomical bladder capacity:
  - EARLY — normal
  - CLASSICAL — reduced

CLASSICAL INTERSTITIAL CYSTITIS

- vesical mucosa:
  - EARLY — normal appearing
  - CLASSICAL — ulcerated, scarred
- submucosal vesical hemorrhages observed following second overdistension

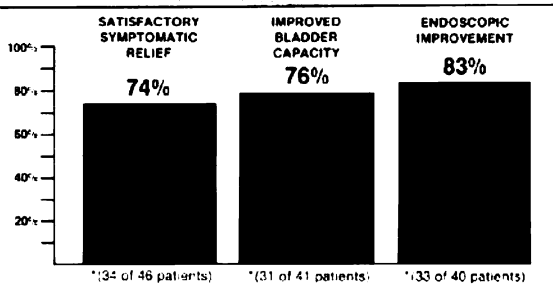
DIAGNOSIS: INTERSTITIAL CYSTITIS

The Solution

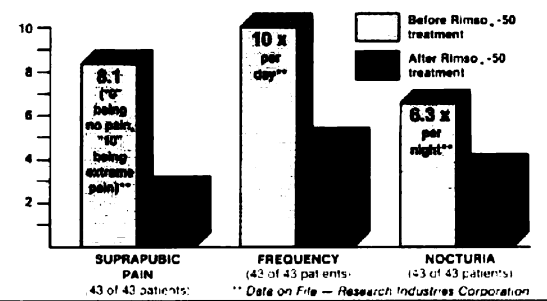
Rimso-50

brand of

STERILE AND PYROGEN-FREE DIMETHYL SULFOXIDE



*STEWART, B.H., et al., J. Urol., 36:116, 1976



** Data on File — Research Industries Corporation

FOR FURTHER INFORMATION WJ12/82

RESEARCH INDUSTRIES CORPORATION
1847 West 2300 South
Salt Lake City, Utah 84119
Toll-Free 1-800-453-8432

Name

Address

City State Zip

Rimso-50

(dimethyl sulfoxide)

50% w/w aqueous solution

INDICATIONS AND USAGE: Rimso-50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. Rimso-50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.

CONTRAINDICATIONS: None known.

WARNINGS: Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical Rimso-50. The physician should be cognizant of this possibility in prescribing Rimso-50. If anaphylactoid symptoms develop, appropriate therapy should be instituted.

PRECAUTIONS: Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations, are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of Rimso-50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation. Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats, and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: A garlic-like taste may be noted by the patient within a few minutes after instillation of Rimso-50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide. The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.

DOSAGE AND ADMINISTRATION: Instillation of 50 ml of Rimso-50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or aseptic syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as lidocaine jelly to the urethra is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately.

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of Rimso-50 can reduce bladder spasm.

In patients with severe interstitial cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia. (Saddle block has been suggested).

HOW SUPPLIED:

Bottles contain 50 ml of sterile and pyrogen-free Rimso-50 (50% w/w dimethyl sulfoxide aqueous solution).

Dimethyl sulfoxide is clear and colorless.

Protect from strong light.

Store at room temperature (15° to 30°C).

Do not autoclave.

NDC #0433-0433-05.

*Stewart, B.H., et al., J. Urol., 36:116, 1976

Rimso-100

brand of

STERILE AND PYROGEN-FREE DIMETHYL SULFOXIDE

CRYOPRESERVATIVE SOLUTION

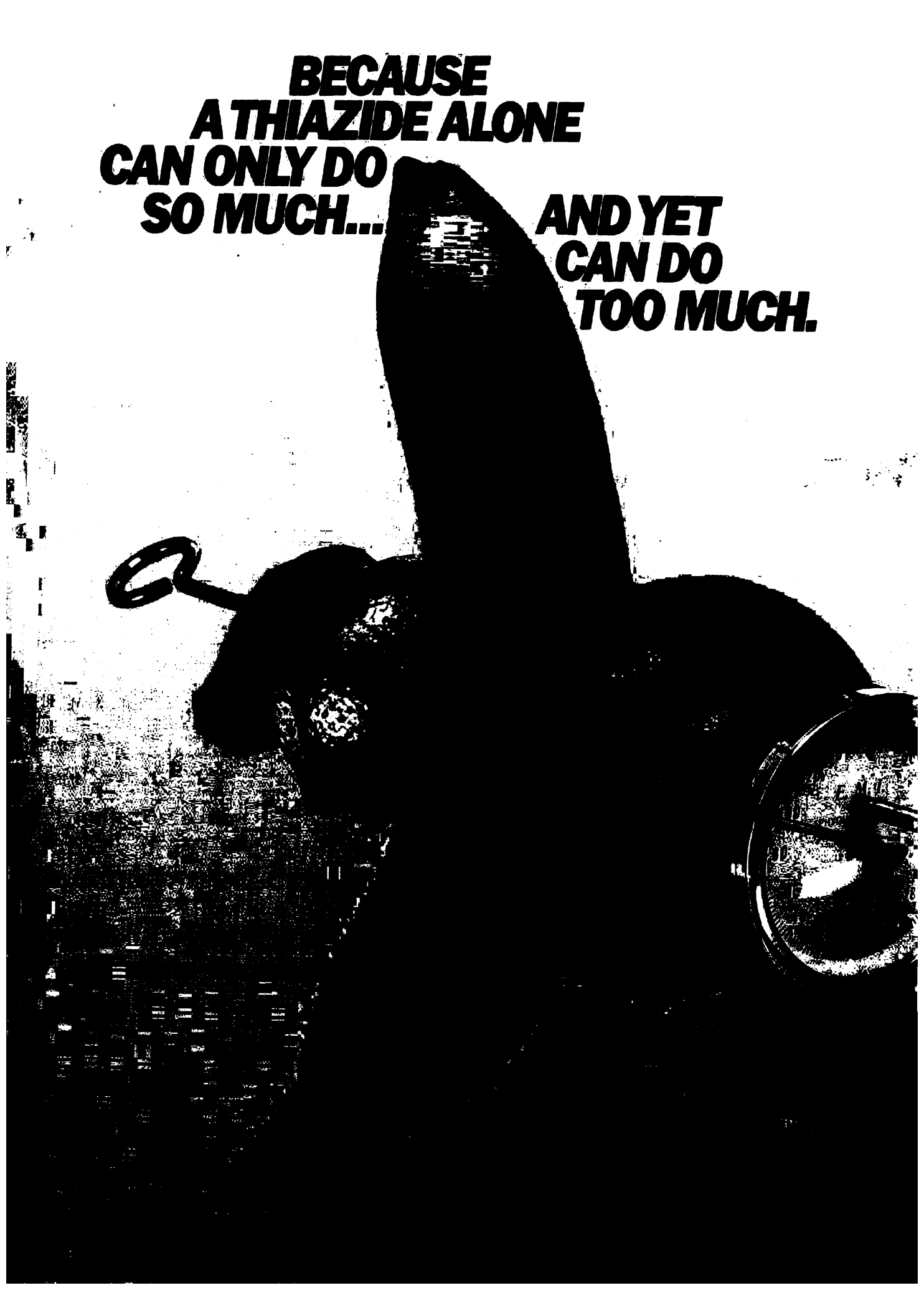
(99.0 - concentration)

Available in:

10 ml ampules, 10 ampules/case
70 ml bottles, 6 bottles/case
70 ml multi-dose containers, 6 bottles/case

BECAUSE A THIAZIDE ALONE CAN ONLY DO SO MUCH...

AND YET CAN DO TOO MUCH.



INCREASE CONTROL WITHOUT INCREASING POTASSIUM PROBLEMS.

A dependable means to long-term blood pressure control.

Many times, a diuretic alone can't keep hypertension in check. INDERIDE, however, can pick up where thiazide therapy leaves off.

The combination of propranolol HCl, the world's most trusted beta blocker, and hydrochlorothiazide, the standard among diuretics, enables INDERIDE to exert an additive antihypertensive effect.[1,2] In fact, a propranolol/hydrochlorothiazide regimen maintained blood pressure below 90 mm Hg in 81.8% to 86.4% of patients followed for 6 to 18 months of therapy.[1]

Low thiazide dosage means reduced risk of hypokalemia.

When thiazides are prescribed in doses greater than 50 mg/day, the potential for hypokalemia increases substantially. What's more, the greater the fall in serum K^+, the greater the risk of hypokalemia-induced PVCs.[3,4]

With INDERIDE, the additive hypotensive effect of propranolol HCl allows the effective dose of hydrochlorothiazide to be kept low (25 mg b.i.d.). And by lowering the daily dose of diuretic, INDERIDE also lowers the potential for diuretic-induced side effects. Potassium problems are less likely to occur—yet blood pressure can be controlled consistently.

INDERIDE®

Each tablet contains INDERAL® (propranolol HCl) 40 mg or 80 mg, and hydrochlorothiazide 25 mg

B.I.D. 40/25 80/25

When you know you need more than a thiazide.

Please see Brief Summary of Prescribing Information on following page.

INDERIDE®

Each tablet contains INDERAL (propranolol HCl) 40 mg or 80 mg, and hydrochlorothiazide 25 mg

B.I.D. 40/25 80/25

NEW TABLET SHAPE ™

The appearance of these tablets is a trademark of Ayerst Laboratories.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERIDE®
BRAND OF
propranolol hydrochloride
(INDERAL®)
and hydrochlorothiazide

No. 484—Each INDERIDE®-40/25 tablet contains:
Propranolol hydrochloride (INDERAL®) . . . . . 40 mg
Hydrochlorothiazide . . . . . 25 mg
No. 488—Each INDERIDE®-80/25 tablet contains
Propranolol hydrochloride (INDERAL®) . . . . . 80 mg
Hydrochlorothiazide . . . . . 25 mg

WARNING: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

INDICATION: INDERIDE is indicated in the management of hypertension. (See boxed warning.)

CONTRAINDICATIONS: Propranolol hydrochloride (INDERAL®): Propranolol hydrochloride is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

Hydrochlorothiazide: Hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to this or other sulfonamide-derived drugs.

WARNINGS: Propranolol hydrochloride (INDERAL®): CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. In patients with impaired renal function, cumulative effects of the drug may develop.

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

USE IN PREGNANCY: Propranolol hydrochloride (INDERAL®): The safe use of propranolol in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: Thiazides appear in breast milk. If the use of the drug is deemed essential, the patient should stop nursing.

PRECAUTIONS: Propranolol hydrochloride (INDERAL®): Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements such as foods with a high potassium content.

Any chloride deficit is generally mild, and usually does not require specific treatment except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration, have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

ADVERSE REACTIONS: Propranolol hydrochloride (INDERAL®): *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Hydrochlorothiazide: *Gastrointestinal:* anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis.

Central Nervous System: dizziness, vertigo, paresthesias, headache, xanthopsia.

Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Cardiovascular, orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions.

Other: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

HOW SUPPLIED: —Each hexagonal-shaped, off-white, scored INDERIDE 40/25 tablet is embossed with an "I" and imprinted with "INDERIDE 40/25," contains 40 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 (NDC 0046-0484-81) and 1,000 (NDC 0046-0484-91). Also in unit dose package of 100 (NDC 0046-0484-99).

—Each hexagonal-shaped, off-white, scored INDERIDE 80/25 tablet is embossed with an "I" and imprinted with "INDERIDE 80/25," contains 80 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 (NDC 0046-0488-81) and 1,000 (NDC 0046-0488-91). Also in unit dose package of 100 (NDC 0046-0488-99).

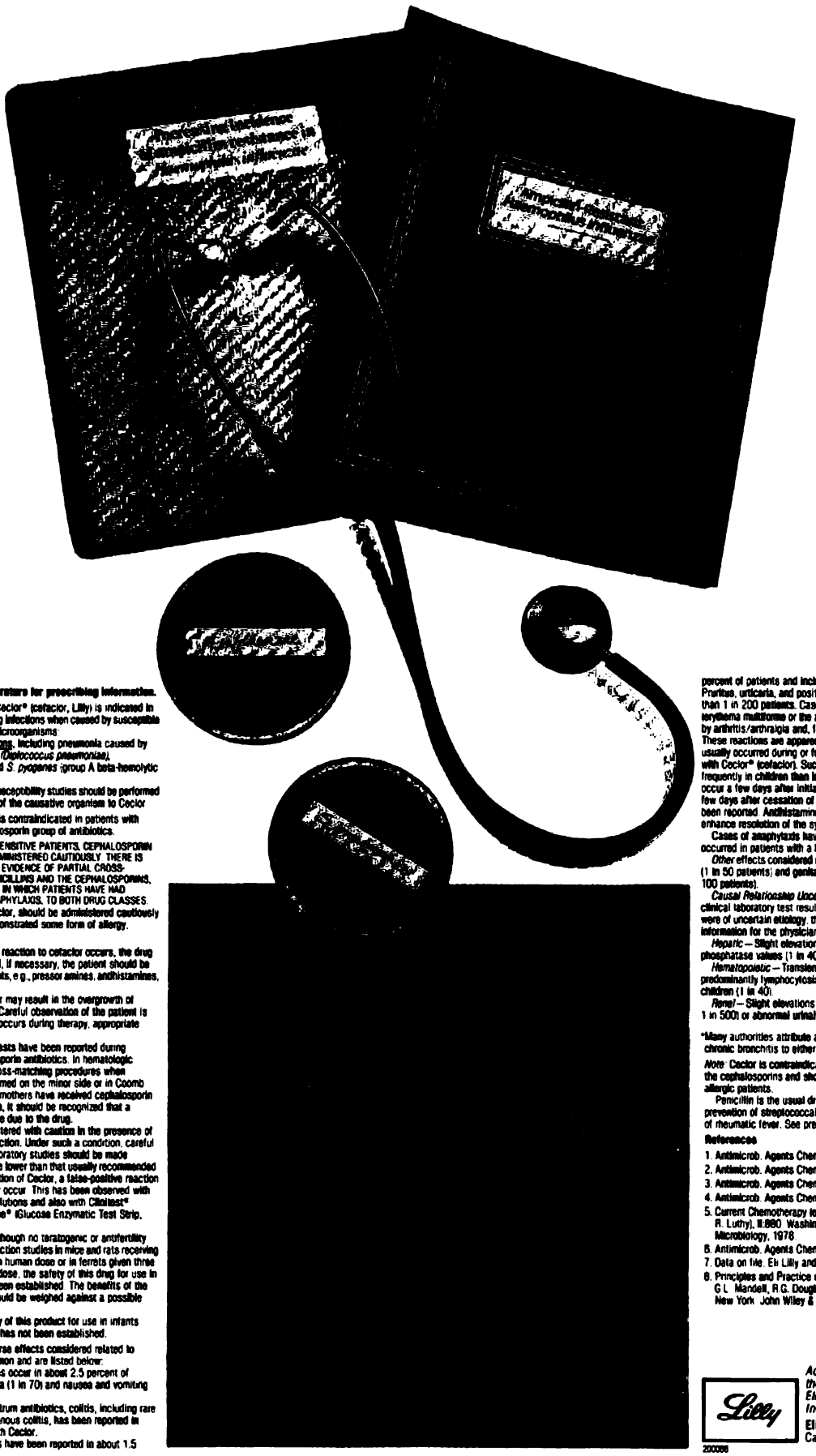
The appearance of these tablets is a trademark of Ayerst Laboratories.

Store at room temperature (approximately 25° C).

7998/882

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

An added complication... in the treatment of bacterial bronchitis*



Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coomb testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Usage in Pregnancy — Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy — Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below:

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90).

As with other broad-spectrum antibiotics, colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with Ceclor.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions, erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor® (cefaclor). Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients); and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). 100286

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[1]

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

References

1. Antimicrob. Agents Chemother., *8*:91, 1975.
2. Antimicrob. Agents Chemother., *11*:470, 1977.
3. Antimicrob. Agents Chemother., *13*:584, 1978.
4. Antimicrob. Agents Chemother., *12*:490, 1977.
5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II:880. Washington, D.C.: American Society for Microbiology, 1978.
6. Antimicrob. Agents Chemother., *13*:861, 1978.
7. Data on file, Eli Lilly and Company.
8. Principles and Practice of Infectious Diseases (edited by G.L. Mandell, R.G. Douglas, Jr., and J.E. Bennett), p. 487. New York: John Wiley & Sons, 1979.

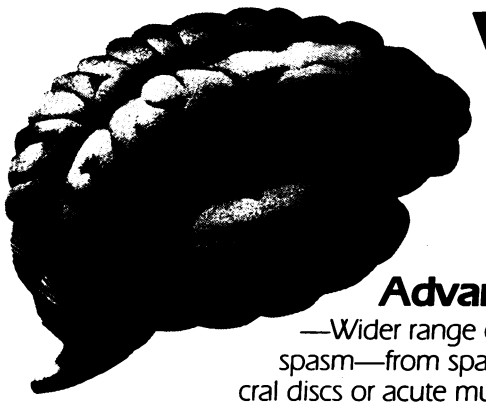
Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

200286

THE SPASM/PAIN/SPASM CYCLE

In skeletal muscle spasm due to local pathology, responsive to the distinct actions of



Adjunctive VALIUM® (IV) diazepam/Roche

2-mg, 5-mg, 10-mg scored tablets

Advantages cyclobenzaprine cannot claim

—Wider range of indications as adjunctive therapy for skeletal muscle spasm—from spasm due to local pathology (*e.g.,* herniated lumbosacral discs or acute muscle strain) to spasm associated with upper motor neuron disorders (*e.g.,* cerebral palsy, athetosis, stiff-man syndrome).

—May be used adjunctively for relieving skeletal muscle spasm in patients with hyperthyroidism, cardiac patients and patients being treated with anticholinergics or guanethidine-type antihypertensives.

—Can be administered to patients less than 15 years and more than 6 months of age.

—Scored tablets in three strengths provide greater dosage flexibility.

Since drowsiness, fatigue and ataxia sometimes occur, patients should be cautioned against driving or operating hazardous machinery and should also be advised against simultaneous ingestion of alcohol.

References: 1. Rankin EA: *Contin Educ 3*(1):46-50, Jan 1975. **2.** When muscle spasm hobbles your patient. *Patient Care 8*(11):20-37, Jun 1, 1974.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium (diazepam/Roche) and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

How Supplied: For oral administration, Valium (diazepam/Roche) scored tablets—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100* and 500;* Prescription Paks of 50, available in trays of 10.* Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25,† and in boxes containing 10 strips of 10.†

*Supplied by Roche Products Inc., Manati, Puerto Rico 00701

†Supplied by Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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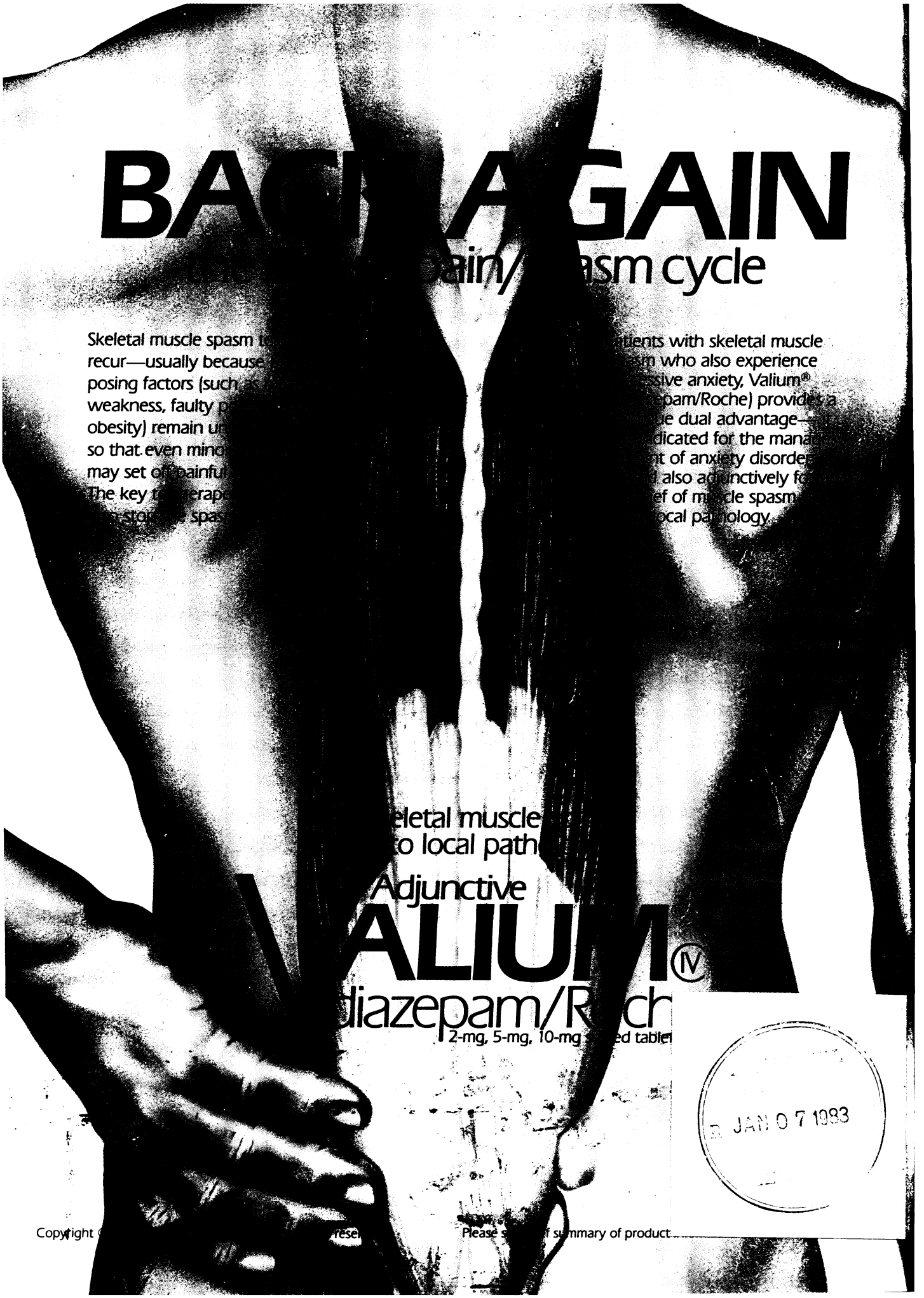
Manati, Puerto Rico 00701



Please s f summary of product

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CHIEF OF MEDICINE
FAMILY PRACTITIONER
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FLIGHT SURGEON
OPHTHALMOLOGIST
OTORHINOLARYNGOLOGIST
PEDIATRICIAN
PEDIATRICIAN/NEONATOLOGIST
RADIOLOGIST
PLASTIC SURGEON
FAMILY PRACTITIONER (OB EXPERIENCE)
PREVENTIVE MEDICINE PHYSICIAN
MEDICAL DIRECTOR (CLINIC-BASED)
GENERAL SURGEON (UROLOGY EXPERIENCE)
INTERNIST (CLINIC-BASED)
CLINIC ADMINISTRATOR (RETIRED M.D.)

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Successful candidates will be offered extremely attractive benefits including a two or three year renewable contract, free accomodations and utilities, life insurance, 59 days leave and holidays, round trip airfare home each year, auto purchase grant plus interest free loan for balance. Extensive sports and recreational facilities.

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PHYSICIANS WANTED

SOUTHERN CALIFORNIA: Two physicians sought for Family Practice opportunity in rapidly growing foothill community. Compensation package includes percentage of net revenues with attractive minimum guarantee. Please respond to Billie Warren, 606 Wilshire Blvd., Suite 416, Santa Monica, CA 90401; or call collect within California (213) 451-5481; 1 (800) 421-6655 outside California.

PULMONARY OR GENERAL INTERNIST: Needed to join another young internist in established practice in Pacific Northwest. Modern community hospitals. Well developed medical community. Outstanding professional, cultural and recreational opportunities. Box 6314, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

HEMATOLOGIST-ONCOLOGIST WANTED—to join two others in well-established subspecialty practice in the Los Angeles area. Board certified or eligible. Excellent salary with unusual opportunity for early partnership. Inquiries and CV to Box 6317, Western Journal of Medicine, 731 Market St., San Francisco, Ca 94103.

RESEARCH ASSOCIATE: Salary $22,000-$25,000; must have PhD or equivalent and at least 2 years post-doctoral training/experience in hybridoma research; background in protein chemistry and membrane biochemistry, immunoassays; knowledge of autoimmunity and cancer biology preferred. An equal opportunity employer. Applicants should apply to: Mary C. Clark, P.O. Box 5816, Stanford, CA 94305.

CALIFORNIA: EMERGENCY OR FAMILY PHYSICIANS—Unique practice opportunity in beautiful North San Diego county. Fee for service; minimum guarantee; malpractice; partnership opportunity. Contact: G. Walls, MD, 167 Spanish Spur, Fallbrook, CA 92028, Phone (714) 723-9468.

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Two well-established internists are seeking an associate. Potential of buying into practice. Highly desirable practice and location in Southern California. Interested individuals are encouraged to respond to

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GENERAL PRACTITIONERS SPECIALISTS—Are you considering a practice change, please call us, let's talk. We have many opportunities in various West Coast locations. If you would like to join a group, associate or own your own practice we can help. (714) 997-0853, or send CV to physicians Search Associates, 1201 W. La Veta, Suite No. 209, Orange, CA 92668.

SANTA BARBARA COUNTY Department of Health Care Services. Primary Care practice in beautiful North Santa Barbara County. Prefer bilingual English-Spanish ability. Salary negotiable. Contact: Barry Williams, MD, Director, Clinical Services, 300 San Antonio Road, Santa Barbara, CA 93110. Phone (805) 967-2311, Ext. 240.

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MEDICAL DIRECTOR OF EMERGENCY UNIT, Presbyterian Hospital—Opportunity for Board Certified/Eligible physician with emergency care skills and interest in medical staff relationships, program development, education, operations, marketing and community relations. Salary/benefits negotiable. Send résumé to George Hunt, Director of Ambulatory Services, Pacific Medical Center, P.O. Box 7999, San Francisco, CA 94120.

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(Continued on Page 42)

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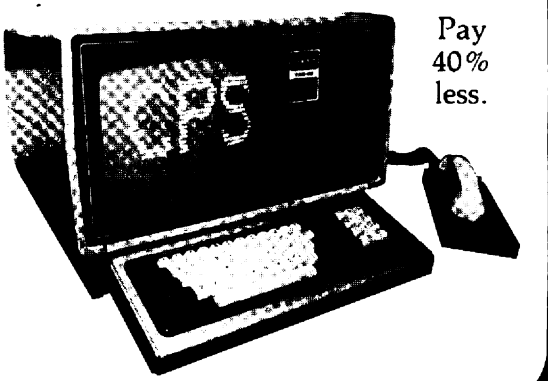

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(Continued from Page 40)

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SITUATIONS WANTED

UROLOGIST. 14 years solo practice same location. Boards, FACS. Desire relocation to S.W., W., N.W. All practice arrangement considered. CV on request. Box 6326, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CALIFORNIA TRAINED INTERNIST—Anxious to return to the Southern West Coast. Currently assistant professor at top midwest university. Box 6297, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST—31, AOA, completing university residency June 1983, seeking practice in northern California/Oregon. CV available. Reply John Jackson, MD, 886 Hilgard Ave., #207, Los Angeles, CA 90024.

BOARD CERTIFIED RADIOLOGIST licensed in California, Oregon, and Washington. Seeking small hospital practice (25-50 beds). Radiology, Nuclear Medicine and Ultrasound. Box 6331, Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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ENGLISH DENTIST wishes to exchange house in California 4-6 weeks summer 1983. Dartmoor National Park, Devonshire. Details: Dr. Hopkins, Penny Meadow, Bridford, South Devon, England. Tel. 0647 52349.

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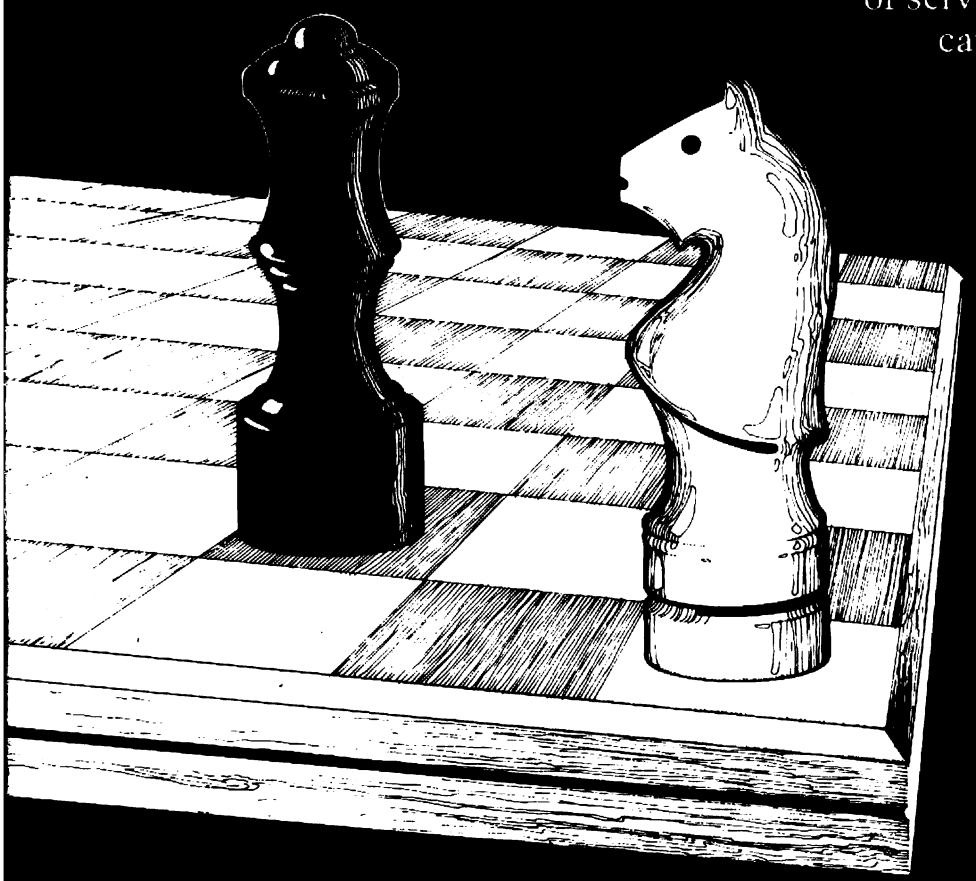

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